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2 The Role of Dopamine in the Control of Locomotor Activity and Reward-Related Incentive Learning

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The neurotransmitter dopamine (DA) acts at a number of terminal regions in the brain including the nucleus accumbens, caudate nucleus and frontal cortex and at a number of different receptor subtypes grouped into the D1- and D2-like families. In general, increases in DA neurotransmission lead to increases in locomotor activity, while decreases in DA neurotransmission lead to decreases in activity. The contribution of DA terminal regions is not uniform, however, and neither is the contribution of receptor subtypes. DA also plays an important and possibly critical role in reward-related incentive learning: In tasks where conditioning occurs to a specific cue, D1-like agonists impair performance whereas D2-like agonists augment performance in many cases. In tasks where conditioning is to contextual cues, D1- and D2-like agonists similarly lead to conditioning. Some recent studies using antagonists show that a block of D1-like receptors may produce a greater effect on reward-related learning than a block of D2-like receptors. Taken together, results suggest a critical role for D1-like receptors in reward-related learning. Animal learning studies have revealed a number of details of the effects of motivational state on the incentive value of primary rewarding stimuli. These effects influence incentive learning. It may be possible to integrate results from psychopharmacological and behavioural studies within the framework of a neuronal model of dopamine-mediated incentive learning involving the modification of corticostriatal synapses activated in close temporal contiguity with the presentation of reward.

KEY WORDS: Dopamine, D1-Like Receptors, Incentive learning, Locomotor activity, Reward

1. INTRODUCTION

A relatively small number of cell bodies located in the region of the ventral midbrain use dopamine (DA) as their neurotransmitter substance. These cells send axons to several forebrain sites including the dorsal and ventral regions of the striatum and the frontal cortex. Their axons branch extensively, each dopaminergic neurone forming hundreds of thousands of synaptic specializations in its terminal region. Although small in number, these elaborately branched cells are in a unique position to modulate connections in the brain between incoming sensory/perceptual messages and outgoing motor signals. In this chapter, we will discuss the role played by these dopaminergic cells in the control of locomotor activity and reward-related incentive learning.

Midbrain dopaminergic neurones often are grouped into two systems. One consists of cell bodies located in the substantia nigra of the midbrain that project primarily to dorsal striatal structures, the caudate and putamen; this system is termed the nigrostriatal system. The other consists of cell bodies located in the ventral tegmental area of the midbrain that project mainly to two regions, the ventral striatal area termed the nucleus accumbens and the medial regions of the frontal cortex; this system is termed the mesolimbic-mesocortical system. For detailed anatomy of these systems see Lindvall (1979). We will review data showing that these two dopaminergic systems play different roles in the control of behaviour (see also chapter 12 by Joel and Weiner).

In recent years it has been found that receptors for DA are of at least five different subtypes. They have been classified into two main families based on the differential effects of DA receptors on the receptor-associated enzyme adenylyl cyclase. DA receptors classified as D1-like are those that stimulate this enzyme, and those classified as D2-like inhibit the enzyme (Kebabian and Calne, 1979; Stoof and Kebabian, 1981). D1-like receptors include the D1 and D5 subtypes and D2-like receptors include the D2, D3 and D4 subtypes (Niznik and Van Tol, 1992; Civelli, Bunzow and Grandy, 1993; Sibley, Monsma and Shen, 1993). We will review findings showing that pharmacological manipulations of these receptor subtypes produces different behavioural effects that suggest a differential contribution of DA receptor subtypes to the control of locomotor activity and learning.

2. DOPAMINE AND LOCOMOTOR ACTIVITY

In general, increases in dopaminergic neurotransmission lead to increases in locomotor activity and decreases in dopaminergic neurotransmission lead to decreases in locomotor activity. However, different terminal regions and different receptor subtypes do not contribute in the same way (for reviews see: Clark and White, 1987; Beninger, Mazurski and Hoffman, 1991).

Locomotion is measured in a variety of ways (Robbins, 1977). Observational techniques include counting crossings of lines painted on the floor of a chamber, or rating scales that rate the level of activation of animals from lying down with eyes closed to vigorous stereotyped activity (Ellinwood and Balster, 1974). There are a number of automated approaches. These include tilt cages fixed on a fulcrum with micro switches under either end that detect movement back and forth over the fulcrum, and jiggle cages set on foam blocks with micro switches under each corner that quantify activity. Many activity monitoring systems use one or more infrared emitters and detectors fixed at various points around the cage to detect movement indicated by beam breaks. Some modern approaches involve creating a digital video record of the animals' movement in the cage and then using sophisticated computer software to analyse a variety of movement-related variables such as distance moved, percentage of time spent moving, rate of movement, movement along walls versus movement in the central region of the cage, etc. Some studies have compared the profile of activational effects of some stimulant drugs as measured by different techniques (for example using a rating scale *versus* infrared emitters and detectors) and have shown that the different approaches yield similar results (Beninger, Cooper and Mazurski, 1985).

One of the agents most commonly used to stimulate locomotor activity is amphetamine, an indirectly-acting DA agonist that stimulates release and blocks uptake (Scheel-Krüger, 1971; Westerink, 1979; Grace, 1991). Although amphetamine affects other neurotransmitters (e.g., norepinephrine) pharmacological studies have shown that its locomotor effects depend on DA (Scheel-Krüger, 1971). Amphetamine produces a dose-dependent increase in locomotion at the low end of the dose-effect curve with locomotor activity decreasing again as doses rise. This latter effect is a result of stereotypy, that is activities in a single place, such as repetitive movements of the head or licking or gnawing behaviour (Ungerstedt, 1979). Systemically injected D2-like agonists such as bromocriptine similarly stimulate locomotor activity at lower doses, and stereotypy at higher doses (Jackson, Jenkins and Ross, 1988). D1-like agonists such as SKF 38393, on the other hand, although having been found to stimulate locomotion in animals, produce less intense effects and do not produce stereotypy like that seen with D2-like agonists (Waddington and O'Boyle, 1989). D1-like agonists but not D2-like agonists have been found to lead to grooming behaviour at higher doses (Molloy and Waddington, 1987). Thus, both D1- and D2-like receptors appear to be involved in the stimulation of locomotor behaviour but stimulation of D2-like receptors leads to larger motor effects.

Since the recent identification of the several members of the D1- and D2-like receptor families, some old and new pharmacological agents have been identified that are relatively specific for one of these receptor subtypes (Sibley, Monsma and Shen, 1993). Some recent studies have evaluated the locomotor effects of agents such as 7-OH-DPAT or PD 128,907 that are somewhat selective for D3 receptors. These agents produced a decrease in locomotor activity at low doses, and an increase at high doses (Daly and Waddington, 1993; Ahlenius and Salmi, 1994). The low dose effects are thought to be mediated by D3 receptors located presynaptically, stimulation of these receptors with a D3 agonist would decrease the release of DA and therefore decrease activity. However, some evidence suggests that there also may be post-synaptic D3 receptors that normally inhibit locomotion, and that direct stimulation of these receptors may contribute to the decreases in locomotion produced by D3 agonists (Svensson, Carlsson and Waters, 1994; Svensson *et al.*, 1994). The discovery of new agents specific for individual receptors in each DA receptor family, and investigations of their behavioural effects are eagerly awaited.

DA receptor antagonists produce decreases in locomotor activity. This effect has been seen with a wide range of DA receptor blockers (Niemegeers and Janssen, 1979). Agents with relative specificity for D1-like receptors such as SCH 23390, and those such as substituted benzamides that are quite specific for D2-like receptors similarly produce decreases in locomotor activity (Beninger, Mazurski, and Hoffman, 1991). As was concluded from studies of agonists with relative selectively for D1- or D2-like receptors, the results of studies with antagonists suggest that both receptor families are involved in the control of locomotor behaviour.

Some studies have evaluated the effects of D1- or D2-like DA receptor antagonists on agonist-induced locomotor activity. In general, antagonists at either D1- or D2-like receptors reduce the stimulant effects of amphetamine or D1- or D2-like receptor-specific agonists (Clark and White, 1987; Beninger, Mazurski and Hoffman, 1991). Thus, for example, the stimulant effects of the D2-like agonist RU24213 were blocked by the D2-like antagonist Ro22-2586 or by the D1-like antagonist SCH 23390 (Pugh

et al., 1985). These and many related observations have led researchers to conclude that D1- and D2-like receptors act in a synergistic manner in the control of locomotor activity (Clark and White, 1987).

The contribution of DA terminal areas has also been studied. Locomotor stimulation, sometimes indicated by contralateral rotation subsequent to unilateral injections (Miller and Beninger, 1991), has been reported following injections of amphetamine into the caudate nucleus (Pycock, 1980), nucleus accumbens (Colle and Wise, 1991; Messier, Mrabet and Destrade, 1991; Messier *et al.*, 1991) or medial frontal cortex (Stewart, Morency and Beninger, 1985). Others, however, have reported no locomotor activation following bilateral intra-frontal cortical injections of amphetamine (Vezina *et al.*, 1991). D1-like agonists produce locomotor stimulation following injection into the nucleus accumbens (Dreher and Jackson, 1989) but are without effect in the caudate nucleus (Smith, Sutton and Beninger, 1997) or frontal cortex (Beninger, Musgrave and Dickson, 1990). D2-like agonists similarly produce locomotor stimulation following injection into the nucleus accumbens (Dreher and Jackson, 1989) and are without effect when injected into the caudate (Smith, Sutton and Beninger, 1997). However, we have found that D2-like agonists injected into the frontal cortex, like amphetamine, produce mild contralateral rotation, an effect consistent with locomotor stimulation (Stewart, Morency and Beninger, 1985; Beninger, Musgrave and Dickson, 1990). Taken together, these results point to both D1- and D2-like receptors in the nucleus accumbens as important for the control of locomotor activity with some contribution from striatal and frontal cortical regions.

It is interesting to note the recent finding that the relatively selective D3 receptor agonist 7-OH-DPAT, when injected into the nucleus accumbens, produced decreased locomotor activity (Gilbert and Cooper, 1995). We have replicated this finding in unpublished studies from our labs. However, there also has been one recent report of an increase in activity (movement time) following microinjections within the accumbens of 7-OH-DPAT (Meyer, 1996). Perhaps the discrepant results relate to the specific dependent measure used. Results suggest that D3 receptors in the nucleus accumbens may inhibit locomotor activity.

The apparent co-operative interaction of D1- and D2-like receptors in the control of locomotor activity that has been described above is not seen in rodents chronically depleted of DA. In rats such depletion is produced with bilateral 6-OHDA lesions of the medial forebrain bundle, after which there is a chronic loss of DA neurons in the ventral midbrain. In these animals, unlike normosensitive animals, D1-like antagonists fail to block the stimulant effects of D2-like agonists and D2-like antagonists fail to block the stimulant effects of D1-like agonists. However, both types of antagonists continue to block the effects of agonists at their own receptor subtype, as expected (Beninger, Mazurski and Hoffman, 1991). Thus, there is an uncoupling of the usual synergistic interaction of D1- and D2-like receptors following chronic DA depletion.

In summary, DA plays an important role in the control of locomotor activity. Both D1- and D2-like receptors are involved, and the nucleus accumbens appears to be a region of considerable importance with some role for the caudate-putamen and frontal cortex. There is a co-operative interaction between D1- and D2-like receptors in normosensitive animals that is lost in animals with supersensitive DA receptors following chronic DA depletion. Preliminary studies of D3 receptors suggest an inhibitory influence on locomotor activity possibly in the nucleus accumbens and possibly at pre-synaptic

DA receptors. Further studies with agents that are relatively selective for DA receptor subtypes are awaited eagerly.

3. DOPAMINE AND CONDITIONED BEHAVIOURS

There is general agreement that DA plays an important and perhaps critical role in reward-related learning (Beninger, 1983, 1993; Wise and Rompré, 1989; LeMoal and Simon, 1991). Behaviours are conditioned by making the presentation of reward contingent upon those behaviours. Thus, for example, the process of training a rat to press a lever involves the shaping of behaviour by presentations of reward for successive approximations of the target response (Skinner, 1938). Eventually, reward is presented only when the desired response is made and the behaviour then has been shaped. One way of describing the learning of lever pressing responses for reward is to emphasize the stimuli that come to control the behaviour. Thus, in the above example, the stimulus lever and other stimuli associated with it (e.g. its place on the wall of the chamber) come to elicit approach and other responses including the lever press.

The role of DA in conditioned behaviours has been studied using a number of paradigms. It is useful and informative to divide those paradigms into two broad categories for the purposes of understanding the effects of manipulations of dopaminergic neurotransmission on reward-related learning. These categories are determined by identifying the stimuli that come to control the behaviour being tested. Tasks like lever pressing form one category which will be termed the *specific cue category*. The defining characteristic of this category is that a specific subset of stimuli from within the experimental environment comes to control behaviour. In the example given above, it was the lever stimulus and related stimuli that came to control approach and other responses, and not other stimuli or places in the test apparatus.

The other category of paradigm will be termed the *contextual category*. The defining characteristic of this category is that the stimuli that come to control behaviour can be the environment itself, not a particular subset of stimuli from within that environment. This type of paradigm would include place conditioning and conditioned activity. In each case, the experimental environment is paired with a rewarding stimulus, usually a drug (but conditioning also occurs with food or water as reward). The test involves an assessment of the time spent in the reward-related place in place conditioning, and simply the level of activity in conditioned activity studies. Unlike lever pressing tasks, there is no need for the animal to make a specific response to a specific subset of stimuli from within the test environment.

It should be noted that the distinction between the specific cue *versus* the contextual categories is being made to provide a basis for understanding the differential behavioural effects of amphetamine *versus* apomorphine and D1- *versus* D2-like agonists in different paradigms. In tasks of the specific cue category it is possible (and likely) that contextual cues acquire some control over behaviour in addition to the control exerted by specific cues. Similarly, in tasks of the contextual category it is possible that a specific feature of the test chamber, for example floor texture, comes to control behaviour. However, the distinction being made between the two task categories has face validity, provides a basis for understanding a large number of pharmacological effects, and makes testable predictions about drug effects in additional paradigms.

Another important consideration is the point in training at which the dopaminergic manipulation takes place. In tasks of the specific cue category, DA receptor agonists or antagonists can be given during the shaping or acquisition period or during responding in trained animals. There are many examples of both approaches in the literature. In tasks of the contextual category, dopaminergic agents can be given during conditioning when the test environment is being paired with reward or during the test phase, when the effects of conditioning are being assessed. In almost all published studies in this category, dopaminergic agents are given during the conditioning phase, not the test.

Two more points of information are needed to provide the background necessary to evaluate the results of studies of dopaminergic agonists and antagonists given to animals trained in tasks of the specific cue or contextual categories. The first is that there is a dopaminergic signal associated with the presentation of a rewarding stimulus to an animal. Thus, dopaminergic neurones have a low tonic level of activity but show bursts of activity when reward occurs (Schultz, Dayan and Montague, 1997). This aspect of dopaminergic neuronal function is discussed in detail in Chapter 2 of this volume (Hyland, 1999). The second point is that dopaminergic neurotransmission can be augmented by agents like amphetamine that enhance release and block uptake (Scheel-Krüger, 1971; Westerink, 1979; Grace, 1991) or by agents like apomorphine that directly stimulate DA receptors (Colpaert, vanBevan and Leysen, 1976); apomorphine stimulates DA receptors of both the D1- and D2-like families (Neve and Neve, 1997). On the one hand, amphetamine at moderate doses would augment the reward signal by increasing the release of DA and prolonging its action in the synapse. On the other hand, apomorphine at doses that lead to a high level of occupation of post-synaptic DA receptors, would mask the DA signal associated with reward. These different mechanisms of action of DA agonists provide valuable insights into the relative contribution of D1- and D2-like receptors to reward-related learning, as discussed in the following sections.

3.1. Dopamine Agonists and Studies in the Specific Cue Category

When animals are trained to lever press for food or water, and are then treated with amphetamine or apomorphine, differential effects are seen. The effects of amphetamine and related drugs have been described as rate-dependent; these compounds enhance low rates of responding and suppress high rates (Harris, Snell and Loh, 1978; Lucki, 1983). In contrast, treatment with apomorphine results in a uniform reduction regardless of baseline rate (Harris, Snell and Loh, 1978). Perhaps when response rates are high, the additional locomotor activation produced by amphetamine leads to a disruption of response organization, resulting in the observed decrease in lever pressing (Robbins, 1981). With respect to the actions of these drugs on low rates of well-trained responding, these findings are consistent with the argument that amphetamine enhances the DA signal produced by reward, whereas apomorphine masks the signal.

Another task in this category is lever pressing for brain stimulation reward (BSR). In this paradigm, both amphetamine and apomorphine have been found to enhance reward (Gallistel and Karras, 1984; Fouriezos and Francis, 1992). This has been seen as leftward shifts in rate-intensity functions, demonstrating reduced thresholds for reward following either of these drugs. These results would appear to be at odds with the differential effects of amphetamine *versus* apomorphine in lever pressing tasks maintained by natural rewards.

Unlike lever pressing for food or water reward, where a natural stimulus is presented contingent upon responding and requires consumatory acts like eating or drinking, BSR reward directly stimulates brain circuits thought to be activated normally by the consumption of natural rewards. *In vivo* voltammetry and microdialysis experiments have shown increased DA release in the nucleus accumbens following either natural rewards or BSR (Phillips, Blaha and Fibiger, 1989; Young and Michael, 1993; Kiyatkin, 1995; Mas, Fumero and Gonzalez-Mora, 1995; Westerink, 1995). However, the speed of onset of the effect is dramatically different for natural rewards versus BSR. Thus, natural rewards produce a gradual increase (Kiyatkin and Gratton, 1994) whereas BSR produces a large and immediate increase in accumbens DA (Phillips, Blaha and Fibiger, 1989). Perhaps the intensity of the DA signal produced by BSR is so great that it cannot be masked by doses of apomorphine that are argued to be effective in masking the weaker signal produced by natural rewards. This provides a basis for understanding the apparently contradictory effects of apomorphine on responding for food or water versus BSR.

Another paradigm in the specific cue category is lever pressing to self-administer drugs. However, almost all of the work with agonists in this paradigm involves using discrete injections of small self-administered volumes as rewarding stimuli, rather than evaluating the effects of experimenter-administered systemic injections of larger volumes and doses. Thus, with either amphetamine or apomorphine the stimulation of DA receptors would be timed to correspond to the period immediately following the response. Usually, there is a stimulus light or other cue that remains on for a period following the response. Presumably, the onset of action of amphetamine or apomorphine would correspond with the presence of this stimulus which would acquire conditioned rewarding properties that then would serve to maintain the response-controlling properties of the lever and related stimuli. It has been found that both amphetamine and apomorphine are self-administered (Pickens and Harris, 1968; Baxter *et al.*, 1974).

A number of studies have evaluated the effects of amphetamine and apomorphine on the acquisition of responding for conditioned reward. Results have shown that amphetamine produces a dose-dependent and selective enhancement of acquisition of pressing a lever that produces a stimulus previously associated with food or water, in a test situation with two levers available (Robbins *et al.*, 1983; Mazurski and Beninger, 1986; Beninger and Ranaldi, 1992). In the same test situation, apomorphine led to a non-specific enhancement of responding on both levers, the control of responding by the conditioned reward being lost (Robbins *et al.*, 1983; Beninger and Ranaldi, 1992). These findings agree with the differential effects of amphetamine and apomorphine on low rates of well-trained lever pressing for food or water that were discussed above. Results support the idea that amphetamine enhances the reward signal while apomorphine masks it.

In recent years, studies similar to those reviewed above have been done to evaluate the effects of D1- versus D2-like agonists. Although agonists at either receptor would be direct-acting like apomorphine, results have shown that D1-like agonists produce apomorphine-like effects whereas D2-like agonists produce amphetamine-like effects! Thus, high rates of lever pressing for food or shock avoidance were decreased by either D1- or D2-like agonists whereas low rates increased following D2-like agonists but decreased following D1-like agonists (see Beninger and Miller, 1998). The reward value of BSR was increased by both D1- and D2-like agonists, as it was with both amphetamine and apomorphine (Ranaldi and Beninger, 1994). Both D1- and D2-like agonists were self-administered (Woolverton, Goldberg and Ginos, 1984; Woolverton, 1986; Wise, Murray

and Bozarth, 1990; Self and Stein, 1992; Weed, Vanover and Woolverton, 1993; Chaperon and Thiébot, 1996). There is one study evaluating the effects of the D1-like agonist SKF 38393 on responding for cocaine self-administration; responding was impaired (Katz and Witkin, 1992). Finally, in conditioned reward studies, D1-like agonists impaired, whereas D2-like agonists enhanced, the acquisition of responding (Beninger and Ranaldi, 1992; Beninger and Rolfe, 1995; Ranaldi, Pantalony and Beninger, 1995).

Taken together, these results show that the response-impairing effects of apomorphine in a number of tasks in the specific cue category are related to its action at D1-like receptors. This suggests a critical role for D1-like receptors in the control of behaviour by rewarding stimuli.

3.2. Dopamine Antagonists and Studies in the Specific Cue Category

Many studies have evaluated the effects of antagonists relatively specific for D1- or D2-like receptors on the tasks discussed in the previous section. In general, effects consistent with a block of reward are seen with agents affecting either DA receptor subtype family (Beninger, Hoffman and Mazurski, 1989; Miller, Wickens and Beninger, 1990; Beninger, 1991, 1993). However, in recent years a number of studies provide results consistent with a greater effect of D1-like antagonists on reward and a greater effect of D2-like antagonists on motor performance. These differences are discussed in detail elsewhere (Beninger and Nakonechny, 1996; Beninger and Miller, 1998) and only an overview will be given here.

In one study, rats reached through an aperture in the cage wall and pressed a pressure transducer for food reward. Treatment with either a D1- or D2-like antagonist led to a decrease in responding, suggestive of a block of the usual effects of reward. However, detailed analyses of the strength of the operant response showed that the decline in response strength was related closely to the decrease in responding for food following the D2-like antagonist but not the D1-like antagonist (Fowler and Liou, 1994). Results suggest that the decrease in responding produced by the D2-like antagonist may have been related to the effects of the drug on motor performance, whereas the effects of the D1-like antagonist were more clearly on reward.

As discussed in the previous section, the acquisition of responding for conditioned reward is enhanced by amphetamine. Treatment with a D1-like antagonist shifted the amphetamine dose-response curve to the right, indicative of a decrease in reward. Of two D2-like antagonists tested, one also shifted the curve to the right but the maximum level of responding seen following treatment with the D1-like antagonist was never seen; the other decreased the amphetamine enhancement of responding in a dose-dependent manner but failed to shift the amphetamine dose-response curve to the right (Ranaldi and Beninger, 1993). These results implicate both D1- and D2-like receptors in the control of responding by conditioned rewards. The results also suggest that D1-like antagonists may produce effects somewhat specific to reward whereas D2-like antagonists affect reward and motor responding, as also suggested by data reviewed above from studies of operant responding for food.

In summary, D1- and D2-like antagonists appear to reduce the effects of reward in a number of tasks in the specific cue category. However, finer analyses suggest that the

actions of D2-like antagonists may be related more closely to their motoric effects, whereas D1-like DA receptor antagonists may reduce reward. (For a further discussion of this dissociation and its possible underlying mechanisms see: Miller, Wickens and Beninger, 1990).

3.3. Dopamine Agonists and Studies in the Contextual Cue Category

In place conditioning experiments, one compartment of a test chamber with two or more compartments is paired with a putative reward over several sessions. In the test, animals are left with access to the entire apparatus and if they spend more time in the compartment paired with a drug or other stimulus, that stimulus is said to be rewarding (Carr, Fibiger and Phillips, 1989; Hoffman, 1989). In this paradigm, both amphetamine and apomorphine have been found to be rewarding (see Hoffman, 1989). Differential effects of these two drugs would not be expected because there are not specific stimuli in the drug-paired environment that must come to control responding. Apomorphine, but not amphetamine, might be expected to impair expression of the conditioned place preference if it was administered on the test day (perhaps after pairing one compartment with food during conditioning) because it might disrupt the selective control of responding by the stimuli from the reward-paired chamber. To our knowledge, this experiment has not been done.

In conditioned activity experiments, a single chamber is paired with a drug or other stimulus (e.g. food) over several days and then a test is given without the drug or other stimulus. The dependent variable is activity level, usually in comparison to a control group that has not received the drug in the test environment. Some have argued that this is an example of classical conditioning, the unconditioned stimulus being the drug, the conditioned stimulus being the drug-paired environment, and activity being the unconditioned response that becomes the conditioned response (Stewart and Eikelboom, 1987). However, Martin-Iverson and Fawcett (1996) have carried out detailed studies of the elements of activity that are produced by the drug *versus* those seen on the drug-free test day and shown that they differ. These results argue against a classical conditioning interpretation of conditioned activity. We favour an interpretation in terms of reward-related learning. Environmental stimuli associated with the drug acquire the ability to elicit approach and other responses that are manifested as increased activity on the test day.

Both amphetamine (Pickens and Crowder, 1967) and apomorphine (Möller, Nowak and Kuschinsky, 1987) have been reported to produce conditioned activity. If the drugs were given on the test day, activity should be seen because of the unconditioned effects of the drug, and since there are no other cues to compete with those paired with the drug, they too may influence activity. The additive effects of the influence of the drug itself and the cues associated with it may augment the drug response, a phenomenon termed sensitization (Stewart, 1992). The possible role of conditioning in sensitization will not be discussed further here.

The effects of D1- and D2-like agonists in these paradigms have been assessed. Like amphetamine and apomorphine, they produce similar effects, in contrast to their differential action in tasks in the specific cue category. Thus, place preference learning has been reported following pairing of one compartment with the D1-like agonist SKF 82958 (Abrahams *et al.*, 1998) or with a number of D2-like agonists (Morency and Beninger,

1986; Hoffman, Dickson and Beninger, 1988; Hoffman and Beninger, 1988, 1989; White, Packard and Hiroi, 1991). Place preference conditioning also was found following the weakly D3-selective agonist 7-OH-DPAT (Mallet and Beninger, 1994; Kling-Petersen *et al.*, 1995b; Chaperon and Thiébot, 1996). However, some researchers failed to find this effect (DeFonseca *et al.*, 1995; Khroyan, Baker and Neisewander, 1995). Moreover, D3 receptor *antagonists* also have been reported to produce a place preference (Richardson *et al.*, 1993; Kling-Petersen *et al.*, 1995a,b). Clearly further studies are needed to resolve the role of D3 receptors in this paradigm. Conditioned activity has been reported following pairing of a test environment with injections of D1- or D2-like agonists (Mazurski and Beninger, 1991).

In summary, D1- and D2-like agonists have similar actions in tasks in the contextual cue category. Thus, agonists acting at either receptor subtype family produce place conditioning and conditioned activity.

3.4. Dopamine Antagonists and Studies in the Contextual Cue Category

Place preference conditioning has been reported for places associated with food, water, psychostimulants or opiates (Carr, Fibiger and Phillips, 1989; Hoffman, 1989). Place preferences based on water or amphetamine were blocked by D1- or D2-like antagonists (Leone and Di Chiara, 1987; Hoffman and Beninger, 1989; Hiroi and White, 1991; Agmo *et al.*, 1993) and place conditioning with morphine was blocked by acute treatment with D1-like antagonists (Bechara and van der Kooy, 1985; Leone and Di Chiara, 1987). These results implicate both DA receptor families in place learning. However, some studies show differential effects. Thus, morphine place conditioning was blocked by chronic systemic or intra-accumbens injections of a D1-like antagonist but not a D2-like antagonist (Shippenberg and Hertz, 1987, 1988; Shippenberg, Bals-Kubik and Herz, 1993) and place conditioning based on cocaine was blocked by a D1- but not by a D2-like antagonist (Cervo and Samanin, 1995). These latter findings suggest that, at least in the case of place conditioning with morphine or cocaine, D1-like receptors may play a more critical role than D2-like receptors.

It should be noted here that the role of DA in opiate reward measured in place conditioning tasks is not straightforward. Van der Kooy and his co-workers have shown that DA antagonists acting at either both receptor families or at the D2-like receptor block morphine or heroin place preferences in opiate-dependent but not in non-dependent animals (Mackey and van der Kooy, 1985; Bechara *et al.*, 1992; Nader *et al.*, 1994). These important observations that there are at least two independent motivational systems and that DA is involved in one but not the other eventually will have to be integrated into our understanding of the role of DA in reward-related learning.

In the above studies reporting that a D1-like antagonist blocked place conditioning, control experiments showed that the same doses of SCH 23390 given alone did not produce a place aversion. However, a number of studies have found that D1-like antagonists, at some doses, produce a place aversion when given systemically (Shippenberg and Herz, 1988; Shippenberg *et al.*, 1991; Acquas and DiChiara, 1994) or into the nucleus accumbens (Shippenberg *et al.*, 1991; Shippenberg, Bals-Kubik and Herz, 1993). In contrast, D2-like antagonists, given alone, failed to produce a place aversion (Shippenberg and Herz, 1988; Shippenberg *et al.*, 1991). Perhaps these results also indicate a more important role for D1- than D2-like receptors in reward.

4. INCENTIVE LEARNING

Stimuli that immediately precede the presentation of a rewarding stimulus acquire the ability to elicit approach and other responses. This form of learning is termed incentive motivational learning, or, more simply, incentive learning, and the stimuli that have acquired response-eliciting properties are termed conditioned incentive motivational stimuli or simply conditioned incentive stimuli (Bolles, 1972; Bindra, 1974; Beninger, 1983). Conditioned incentive stimuli also acquire the ability themselves to act as rewarding stimuli, changing the ability of stimuli that signal them to elicit approach and other responses. For this reason, conditioned incentive stimuli sometimes are referred to as conditioned rewards.

Incentive learning is reward-related learning. Thus, DA plays an important and perhaps critical role in incentive learning. In a number of previous papers, and in the arguments presented in the previous section, we and others have suggested that it is DA acting at D1-like receptors that is critical for incentive learning (Miller, Wickens and Beninger, 1990; Wickens, 1990, 1993; Beninger, 1991, 1992, 1993; Beninger and Ranaldi, 1994; Kötter, 1994; Wickens and Kötter, 1995; Beninger and Nakonechny, 1996; Beninger and Miller, 1998; Josselyn, Miller and Beninger, 1997). Details of the mechanism can be found in these references. For the purposes of the present discussions, we will focus on some of the elements of learning, but not the possible intracellular biochemical mechanisms that may mediate the plastic changes in synaptic connections underlying incentive learning. This latter material is covered in the above references.

In this section we will begin by reviewing the possible interaction of dopaminergic and glutamatergic afferents to the striatum (including the nucleus accumbens) that underlies incentive learning. We then will review some recent studies from animal learning laboratories that provide further details about the role of motivation in incentive learning. Finally, we will assess the implications of these findings for our neuronal model of incentive learning.

4.1. Dopaminergic-Glutamatergic Interactions in Incentive Learning

The heaviest projection area of the cortex is to the striatum, and the corticostriatal neurones are glutamatergic (Graybiel *et al.*, 1994). They co-terminate on the dendrites of medium spiny striatal neurons along with dopaminergic afferents (Smith and Bolam, 1990). It is at these co-terminal regions that the synaptic interactions underlying incentive learning are thought to occur (Beninger, 1993; Kötter, 1994; Wickens and Kötter, 1995).

The striatum can be viewed as an interface between sensory/perceptual regions of the brain and motor output regions. From this point of view, various stimuli in the environment of an animal are thought to be represented by the activation of a specific set of neurones in the cortex and therefore a specific set of corticostriatal afferents. In the striatum, these afferents synapse on output neurones which influence motor behaviour via projections to the thalamus (projecting in turn to the cortex) and via projections to brainstem areas (that project in turn to motor regions) (Graybiel *et al.*, 1994).

Dopaminergic neurones branch extensively in the striatum (see Beninger, 1993) and contact medium spiny neurones on the same dendrites that have glutamatergic terminals (Smith and Bolam, 1990). With this arrangement of connections, the dopaminergic system is situated perfectly to modulate the strength of glutamatergic corticostriatal

projections. Since striatal output influences motor behaviour, DA may modulate the ability of various stimuli to elicit responses. It now is well established that biologically important stimuli, including reward, activate dopaminergic neurones (Schultz, Dayan and Montague, 1997). When reward occurs, the release of DA could lead to a change in the strength of corticostriatal synapses that were activated recently by the stimuli present in the environment associated with reward.

This model of synaptic events associated with incentive learning is presented in Figure 2.1. A single line is used to represent the corticostriatal afferents activated by a particular stimulus although in reality many axons would be involved. Similarly, only a single dopaminergic axon is shown. In panel A, the synapse between afferents activated by the stimulus aspects of food and striatal medium spiny neurones is blackened to indicate that it has been strengthened by previous conditioning. In panel B, a lever is being pressed, activating striatal projections of cortical neurones that were stimulated by presentation of that lever stimulus. In panel C, food is presented immediately following the lever press; striatal projections of cortical neurones activated by the stimulus aspects of food are active as are dopaminergic neurones activated by reward. We suggest that DA acting at D1-like receptors alters the strength of the most recently activated corticostriatal glutamatergic synapses. The mechanism for storing information about recent activity and for altering synaptic effectiveness has been discussed in detail elsewhere (Beninger, 1993; Kötter, 1994; Wickens and Kötter, 1995; Wickens, chapter 4 of this volume). In panel D, the lever now is a conditioned incentive stimulus with an enhanced ability to influence striatal output.

This model forms the basis of a putative neuronal mechanism that underlies the ability of rewarding stimuli to modify behaviour, i.e. to produce learning. In recent years, researchers who study animal learning have identified a number of motivational influences on incentive learning. These studies have focused on the incentive value of the primary reward itself rather than the incentive value of stimuli associated with reward. In the next section, this work will be reviewed briefly. Following that, these new findings will be considered from the point of view of the above model in an attempt to begin to bring together two current lines of study of incentive learning that at present have not been integrated.

4.2. Motivational Influences on Incentive Learning

Dickinson and Balleine (1994) have proposed that motivational states control instrumental responding indirectly through their effects on the primary incentive value of rewarding stimuli. They refer to this process as incentive learning and relate it to Tolman's (1949) formulation of cathexis. Both accounts propose that the primary incentive value of a reward itself in a given motivational state must be learned through experience or contact with the reward in the relevant motivational state.

One study presents experimental evidence that alterations in motivational state, which decrease the value of food reward, change the incentive value of stimuli controlling responding (Balleine and Dickinson, 1991). In this experiment, animals were trained to lever press for a sucrose solution, which then was devalued by a lithium chloride injection that induced nausea. Subsequent performance of the instrumental action in an extinction test was reduced; however, *this effect occurred only if animals were re-exposed to the*

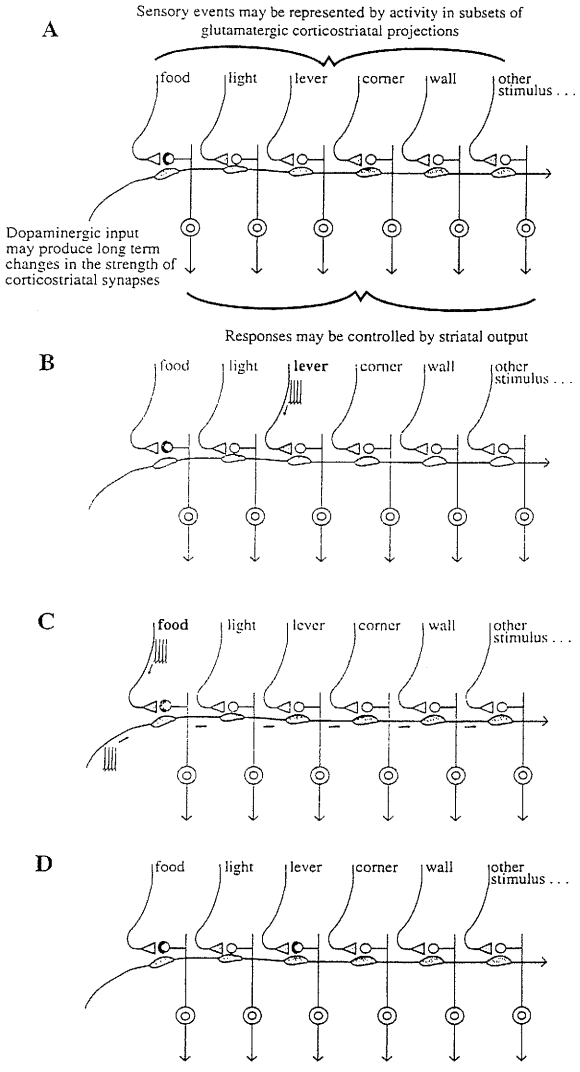

Figure 2.1. Possible synaptic events associated with incentive learning. **A**: Descending projections represent corticostriatal glutamatergic neurones that are activated by particular environmental stimuli; although each stimulus is represented by one neurone, presumably many neurones are activated by a particular stimulus. Medium spiny output neurones of the striatum are thought to control responses. Dopaminergic projections to the input-output interface are represented by a single neurone. It is proposed that dopaminergic inputs activated by rewarding stimuli produce long term changes in the strength of corticostriatal synapses. The synaptic darkening on the terminal from the cortical efferent activated by the stimulus properties of food represents synaptic strengthening previously produced by incentive learning. **B**: When the lever is pressed, the stimulus aspects of the lever activate cortical neurones that project to the striatum. **C**: If food follows the lever press response, the stimulus aspects of food activate the associated cortical efferents, and the reward properties of food activate the dopaminergic striatal afferents. Dopamine is thought to produce a long term change in the strength of the most recently active corticostriatal synapses (Beninger, 1993). **D**: Incentive learning, involving an increase in the ability of the stimulus aspects of the lever to control responding, is represented by the synaptic darkening in the corticostriatal synapse activated by the lever.

sucrose solution prior to testing. Furthermore, the effect was specific to the outcome associated with the instrumental action. Thus, re-exposure to the devalued outcome selectively attenuated performance of the action trained with that outcome, relative to other actions trained with different outcomes.

Using similar experimental procedures, Dickinson and colleagues have shown that alterations of other motivational variables similarly change the incentive value of stimuli controlling responding. This effect has been seen following changes in food deprivation (Balleine, 1992; Balleine, Ball, and Dickinson, 1994), a decrement in water deprivation (Lopez, Balleine, and Dickinson, 1992), a shift between rather than within motivational states (Dickinson and Dawson, 1988, 1989), and the induction of drug states (Balleine, Ball, and Dickinson, 1994). It is important to note that *pre-exposure* to a primary rewarding stimulus while in a non-deprived state, for example, followed by training while deprived, and then testing in extinction while again non-deprived, similarly led to reduced responding compared to non-pre-exposed animals (Balleine, 1992). Thus, experience with the primary reward while at one level of deprivation can influence responding in extinction following training at another level of deprivation whether that experience preceded or followed training.

The finding that shifts in food deprivation lead to changes in responding only if animals are pre- or re-exposed to the primary incentive stimulus while in the changed motivational state is of particular interest. This is so because these findings indicate that motivational states do not determine directly the primary incentive value of stimuli that fulfil basic biological needs. Thus, the incentive value of primary rewards such as food, as they relate to a particular motivational state, must be learned through direct contact with the stimulus in that state.

Further studies examined the physiological mechanisms by which hunger controls the assignment of incentive value to a food reward. Consistent with their previous findings, Balleine and Dickinson (1994) found that animals that were trained concurrently with two actions and two outcomes in a deprived state and then re-exposed to one of the outcomes in a non-deprived state, exhibited reduced levels of the action associated with the re-exposed outcome during an extinction test while in a non-deprived state. They then evaluated the effects of blockade of endogenous cholecystokinin (CCK), a peptide thought to modulate the effects of food deprivation on motivation to eat (Beinfield, 1995). Administration of devazepide (a CCK receptor antagonist specific for a subtype known as CCK_A receptors), during re-exposure reduced the usual effects of re-exposure on responding. Conversely, the increased incentive value of a food reward produced by a shift from a non-deprived to a deprived state was blocked by injections of exogenous CCK during the re-exposure phase in a deprived condition (Balleine, Davies and Dickinson, 1995). Thus, the ability of a change in food deprivation to alter the primary incentive value of food is mediated by changes in CCK levels.

In related experiments, devaluation, produced by re-exposure to a stimulus previously paired with a lithium chloride injection, was blocked by administration of the anti-emetic ondansetron (Balleine, Garner, and Dickinson, 1995). This finding suggests that feedback consequences of the re-exposed stimulus are critical for incentive learning.

Balleine, Ball and Dickinson (1994) argue that the feedback signals about the animal's motivational state determine the assignment of primary incentive value to rewarding stimuli by modulating affective or hedonic reactions to the stimulus. This hypothesis is based on their finding that the incentive value of a food reward is increased during incentive learning

when animals experience the food under the influence of the benzodiazepine agonist midazolam (Balleine, Ball, and Dickinson, 1994). Benzodiazepines enhance positive ingestive reactions to food (Berridge and Treit, 1986), and midazolam also increases the incentive value of a non-nutritive saccharin solution. The authors of the Balleine *et al.* study argue that, since the animals in that study were not food deprived, the incentive learning effect was probably not mediated by feedback from post-ingestional properties of the food. Rather, they propose that incentive learning involves the formation of an association between the animal's current motivational state and the affective properties of the goal object, which themselves are determined by that motivational state.

In summary, according to the work of Dickinson and colleagues, when motivational states control instrumental responding indirectly through their modulation of the incentive value of primary rewarding stimuli, incentive learning is defined to occur. This effect is seen when animals are given exposure to a rewarding stimulus while in one motivational state, trained to respond for the same reward when in another state, and then tested in extinction in the original motivational state. Some of the physiological mechanisms subserving these effects have been identified.

4.3. Understanding Motivational Influences on Incentive Learning from the Point of View of the Neuronal Model of Incentive Learning

The recent studies of Dickinson and his colleagues (reviewed above) provide valuable insights into the relationships that control incentive learning. At present it is not possible to integrate all of these findings into the neuronal model for incentive learning that has been proposed (see Figure 2.1). However, some links can be found, and speculation about others is possible. These links will be discussed in this section.

We begin by considering the pre- and re-exposure experiments, involving a change in the level of food deprivation. If an animal is trained to lever press for food while food deprived, and is then tested in extinction while no longer food deprived, it will press at the same level as a food-deprived animal unless it has been re-exposed to the food while in the non-deprived state. On the one hand, if the animal has not experienced the food in the non-deprived state and is tested in extinction while non-deprived, previous incentive learning should be intact and the lever and related stimuli will control responding. Hence, no difference is seen between deprived and non-deprived animals. On the other hand, if food is experienced while in the non-deprived state, less responding is seen subsequently in extinction.

To understand the possible neuronal connections underlying this incentive learning effect, the role of DA in incentive learning *versus* stimulus-stimulus associative learning is important to note. Thus, there is plenty of evidence that animals treated with DA receptor blocking drugs, or depleted of DA, can learn relationships between or among stimuli (Beninger, 1983), although in these animals, stimuli associated with reward do not come to control responding. The results of the motivational shift experiments, involving training while food-deprived and testing in extinction while no longer food deprived, might be understood as follows. A number of assumptions are necessary. First of all, the cells activated by the stimulus properties of food when food is experienced while food-deprived and those activated by food when it is experienced in a non-deprived state must be different. Those cells activated by food, experienced while food-deprived, must acquire stronger response-eliciting (incentive) properties. The two different sets of

cells activated by food experienced in different states of deprivation are assumed to be connected by stimulus-stimulus associative learning.

When training occurs while food-deprived, the stimulus properties of food are strong incentive stimuli and the lever stimulus acquires strong incentive properties (see Figure 2.1). By stimulus-stimulus learning the lever stimulus and stimulus properties of food (while in a food-deprived state) would become associated. The responding in extinction of non-food-deprived animals, without previous experience of food while not food-deprived, would be controlled by the incentive properties of the lever. Responding may also be influenced by the incentive properties of the cells responding to the stimulus properties of food when food-deprived, these being associatively activated. For the animals with previous experience of food while non-deprived, the cells associatively activated most strongly in response to stimulus aspects of the lever might be those normally responding to the stimulus aspects of food while in a non-deprived state. These cells would have weaker incentive properties and as a result less responding may occur.

We acknowledge the speculative nature of the above explanation. However, the studies of Dickinson and Balleine and others make it clear that motivational states do not influence directly the level of responding, but rather do so indirectly by modulating the incentive value of rewarding and reward-related stimuli. It is challenging to explain the finding that *pre-exposure* to food while non-deprived influences responding in extinction while not deprived, after training while deprived. This is because the lever-related stimuli have no association with a non-food-deprived state prior to extinction testing. Only the primary rewarding stimulus–food–was associated previously with non-deprivation. Thus, there must be a means for prior information about the incentive quality of food while non-deprived to influence the ability of the lever to control responding. The proposed relationship provides one possibility. This explanation would apply similarly to studies in which other motivational systems were altered or where animals went from being less to more food-deprived.

The finding that CCK may play a role in the effects of food deprivation on incentive learning provides valuable details of the possible physiological and neuronal mechanisms that may underlie these effects. Based on their finding that midazolam, a benzodiazepine that would augment GABAergic neurotransmission, increased the incentive value of food reward, Balleine *et al.* (1994) suggested that incentive learning involves the formation of an association between the animal's current motivational state and the affective properties of the goal object, which themselves are determined by that motivational state. From the present point of view, we would speculate that food in the presence of midazolam leads to a larger DA signal, and therefore to stronger incentive learning represented by the strength of glutamatergic cortico-striatal synapses. To our knowledge, *in vivo* studies have not assessed the possible interactions of benzodiazepines with DA release produced by food.

5. SUMMARY AND CONCLUSIONS

In this chapter we have provided an overview of some of the recent studies of the role of DA in the control of locomotor activity and reward-related incentive learning. In locomotor control, both D1- and D2-like receptors are involved, and the nucleus accumbens

appears to be a region of considerable importance; the caudate-putamen and frontal cortex also may play a role. There is a co-operative interaction between D1- and D2-like receptors in normosensitive animals that is lost in animals with supersensitive DA receptors following chronic DA depletion. Preliminary studies of D3 receptors suggest an inhibitory influence on locomotor activity possibly in the nucleus accumbens, and possibly at pre-synaptic DA receptors. Further studies with agents that are relatively selective for DA receptor subtypes are awaited eagerly.

For reward-related learning, tasks were divided into the "specific cue" and "contextual" categories. Lever pressing tasks were included in the former category. In tasks of this category, amphetamine generally increased responding whereas apomorphine impaired responding. The response-impairing effects of apomorphine appeared to be related to its action at D1-like receptors. D1- and D2-like antagonists appeared to reduce the effects of reward in a number of these tasks. However, finer analyses suggest that the actions of D2-like antagonists may be related more closely to their motoric effects whereas D1-like DA receptor antagonists may reduce reward. These results suggested a critical role for D1-like receptors in the control of behaviour by rewarding stimuli.

Tasks in the contextual cue category include place conditioning and conditioned activity. Like amphetamine and apomorphine, D1- and D2-like agonists have similar actions in these tasks, producing rewarding effects in place conditioning, and producing conditioned activity. Antagonists at either receptor family block the effects of reward in place conditioning tasks and block conditioned activity. Some findings suggest that, at least in the case of place conditioning with morphine or cocaine, D1-like receptors may play a more critical role than D2-like receptors. These results implicate both DA receptor families in place learning and conditioned activity, and some results suggest a more important role for D1-like receptors.

The second major section of this chapter reviewed theories of incentive learning. A neuronal model involving dopaminergic-glutamatergic interactions in the striatum was reviewed as a basis for understanding the role of DA in reward-related learning and the contribution of D1-like receptors.

The studies of Dickinson and his colleagues were reviewed, focusing on their idea that motivational states control instrumental responding indirectly through their effects on the primary incentive value of rewarding stimuli. For example, devaluation studies revealed that responding in extinction was reduced following a reduction in food deprivation only if food was experienced in the deprived state prior to the extinction test. Further studies identified some of the physiological variables mediating these effects.

We attempted to integrate the animal learning studies of incentive learning with the psychopharmacological ones that suggested the dopamine-glutamate interaction model. A role for both incentive and stimulus-stimulus associative learning was identified. At present, there continues to be a need to seek a common language and mechanism for understanding the variety of results that these lines of study have produced.

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REFERENCES

Abrahams, B.S., Rutherford, J.D., Mallet, P.E. and Beninger, R.J. (1998) Place conditioning with the dopamine D1-like agonist SKF 82958 but not SKF 81297 or SKF 77434. *European Journal of Pharmacology*, **343**, 111–118.

Acquas, E. and DiChiara, G. (1994) D1 receptor blockade stereospecifically impairs the acquisition of drug-conditioned place preference and place aversion. *Behavioural Pharmacology*, **5**, 555–569.

Agmo, A., Federman, I., Navarro, V., Padua, M. and Velazquez, G. (1993) Reward and reinforcement produced by drinking water: Role of opioids and dopamine receptor subtypes. *Pharmacology Biochemistry and Behavior*, **46**, 183–194.

Ahlenius, S. and Salmi, P. (1994) Behavioral and biochemical effects of the dopamine D–3 receptor-selective ligand, 7-OH-DPAT, in the normal and the reserpine-treated rat. *European Journal of Pharmacology*, **260**, 177–182.

Balleine, E. (1992) Instrumental performance following a shift in primary motivation depends on incentive learning. *Journal of Experimental Psychology: Animal Behavior Processes*, **18**, 236–250.

Balleine, B., Ball, J., and Dickinson, A. (1994). Benzodiazepine-induced outcome revaluation and the motivational control of instrumental action in rats. *Behavioral Neuroscience*, **108**, 573–589.

Balleine, B., Davies, A. and Dickinson, A. (1995) Cholecystokinin attenuates incentive learning in rats. *Behavioral Neuroscience*, **109**, 312–319.

Balleine, B. and Dickinson, A. (1991). Instrumental performance following reinforcer devaluation depends upon incentive learning. *The Quarterly Journal of Experimental Psychology*, **43**, 279–296.

Balleine, B. and Dickinson, A. (1994). Role of cholecystokinin in the motivational control of instrumental action in rats. *Behavioral Neuroscience*, **108**, 590–605.

Balleine, B., Garner, C. and Dickinson, A. (1995). Instrumental outcome devaluation is attenuated by the anti-emetic ondansetron. *The Quarterly Journal of Experimental Psychology*, **48B**, 235–251.

Baxter, B.L., Gluckman, M.I., Srein, L. and Scerni, R. (1974) Self-injection of apomorphine in the rat: Positive reinforcement by a dopamine receptor stimulant. *Pharmacology Biochemistry and Behavior*, **2**, 387–391.

Bechara, A., Harrington, F., Nader, K. and van der Kooy, D. (1992) Neurobiology of motivation: Double dissociation of two motivational mechanisms mediating opiate reward in drug-naive versus drug-dependent animals. *Behavioral Neuroscience*, **106**, 798–807.

Bechara, A. and van der Kooy, D. (1985) Opposite motivational effects of endogenous opioids in brain and periphery. *Nature*, London, **314**, 533–534.

Beinfield, M.C. (1995). Cholecystokinin/Gastrin. In *Psychopharmacology: The Fourth Generation of Progress*, F.E. Bloom and D.J. Kupfer (eds), New York: Raven Press, pp. 585–594.

Beninger, R.J. (1983) The role of dopamine in locomotor activity and learning. *Brain Research Reviews*, **6**, 173–196.

Beninger, R.J. (1991) Receptor subtype-specific dopamine angonists and antagonists and conditioned behaviour. In *The mesolimbic dopamine system: From motivation to action*, edited by P. Willner and J. Scheel-Krüger. Chichester: John Wiley and Sons, pp. 273–299.

Beninger, R.J. (1992) D–1 receptor involvement in reward-related learning. *Journal of Psychopharmacology*, **6**, 34–42.

Beninger, R.J. (1993) Role of D1 and D2 receptors in learning. In *D1:D2 Dopamine Receptor Interactions: Neuroscience and Pharmacology*, edited by J. Waddington, London: Academic Press, pp. 115–157.

Beninger, R.J., Cooper, T.A. and Mazurski, E.J. (1985). Automating the measurement of locomotor activity. *Neurobehavioral Toxicology and Terratology*, **7**, 79–85.

Beninger, R.J., Hoffman, D.C. and Mazurski, E.J. (1989) Receptor\ subtype-specific dopaminergic agents and conditioned behavior. *Neuroscience and Biobehavioral Reviews*, **13**, 113–122.

Beninger, R.J., Mazurski, E.J. and Hoffman, D.C. (1991) Receptor subtype-specific dopaminergic agents and unconditioned behavior. *Polish Journal of Pharmacology and Pharmacy*, **43**, 507–528.

Beninger, R.J. and Miller, R. (1998) Dopamine D1-like receptors and reward-related incentive learning. *Neuroscience and Biobehavioral Reviews*, **22**,335–345.

Beninger, R.J., Musgrave, M.A. and Dickson, P.R. (1990) Unilateral injections of a D2 but not D1 agonist into the frontal cortex of rats produce a contralateral directional bias. *Pharmacology Biochemistry and Behavior*, **37**, 387–392.

Beninger, R.J. and Nakonechny, P.L. (1996) Dopamine D_1-like receptors and molecular mechanisms of incentive learning. In *Dopamine Disease States*, R.J. Beninger, T. Palomo and T. Archer (eds), Madrid: CYM Press, pp. 407–431.

Beninger, R.J. and Ranaldi, R. (1992) The effects of amphetamine, apomorphine, SKF 38393, quinpirole and bromocriptine on responding for conditioned reward in rats. *Behavioural Pharmacology*, **3**, 155–163.

Beninger, R.J. and Ranaldi, R. (1994) Dopaminergic agents with different mechanisms of action differentially affect responding for conditioned reward. In *Strategies for studying brain disorders: Vol 1. Depressive, anxiety and drug abuse disorders*, T. Palomo and T. Archer (eds), London: Farrand Press, pp. 411–428.

Beninger, R.J. and Rolfe, N.G. (1995) Dopamine D1-like receptor agonists impair responding for conditioned reward in rats. *Behavioural Pharmacology*, **6**, 785–793.

Berridge, K.C., and Treit, D. (1986). Chlordiazepoxide directly enhances positive ingestive reactions. *Pharmacology, Biochemistry and Behavior*, **24**, 217–221.

Bindra, D. (1974). A motovational view of learning, performance and behavior modification. *Psychological Review*, **81**, 199–213.

Bolles, R.C. (1972) Reinforcement, expectancy, and learning. *Psychological Review*, **79**, 394–407.

Carr, G.D., Fibiger, H.C. and Phillips, A.G. (1989). Conditioned place preference as a measure of drug reward. In *The Neuropharmacological Basis of Reward*, J.M. Liebman and S.J. Cooper (eds), Oxford: Clarendon Press, pp. 264–319.

Cervo, L. and Samanin, R. (1995) Effects of dopaminergic and glutamatergic receptor antagonists on the acquisition of cocaine conditioned place preference. *Brain Research*, **673**, 242–250.

Chaperon, F. and Thiébot, M.-H. (1996) Effects of dopaminergic D_3-receptor-preferring ligands on the acquisition of place conditioning in rats. *Behavioural Pharmacology*, **7**, 105–109.

Civelli, O., Bunzow, J.R. and Grandy, D.K. (1993) Molecular diversity of the dopamine receptors. *Annual Reviews of Pharmacology and Toxicology*, **32**, 281–307.

Clark, D. and White, F.J. (1987) Review: D1 dopamine receptor–the search for a function: A critical evaluation of the D1/D2 dopamine receptor classification and its functional implications. *Synapse*, **1**, 347–388.

Colle, L.M. and Wise, R.A. (1991) Circling induced by intra-accumbens amphetamine injections. *Psychopharmacology*, **105**, 157–161.

Colpaert, F.C., vanBevan, W.F.M. and Leysen, J.E.M.P. (1976) Apomorphine: Chemistry, pharmacology, biochemistry. *International Review of Neurobiology*, **19**, 225–268.

Daly, S.A. and Waddington, J.L. (1993) Behavioural effects of the putative D–3 dopamine receptor agonist 7-OH-DPAT in relation to other 'D–2-like' agonists. *Neuropharmacology*, **32**, 509–510.

DeFonseca, F.R., Rubio, P., MartinCalderon, J.L., Caine, S.B., Koob, G.F. and Navarro, M. (1995) The dopamine receptor agonist 7-OH-DPAT modulates the acquisition and expression of morphine-induced place preference. *European Journal of Pharmacology*, **274**, 47–56.

Dickinson, A. and Balleine, B. (1994) Motivational control of goal-directed action. *Animal Learning and Behavior*, **22**, 1–18.

Dickinson, A., and Dawson, G.R. (1988). Motivational control of instrumental performance: The role of prior experience of the reinforcer. *The Quarterly Journal of Experimental Psychology*, **40B**, 113–134.

Dickenson, A. and Dawson, G.R. (1989) Incentive learning and the motivational control of instrumental performance. *Quarterly Journal of Experimental Psychology*, **41B**, 99–112

Dreher, J.K. and Jackson, D.M. (1989) Role of D_1 and D_2 dopamine receptors in mediating locomotor activity elicited from the nucleus accumbens of rats. *Brain Research*, **487**, 267–278.

Ellinwood, E.H. and Balster, R.L. (1974) Rating the behavioral effects of amphetamine. *European Journal of Pharmacology*, **28**, 35–41.

Fouriezos, G. and Francis, S. (1992) Apomorphine and electrical self-stimulation of rat brain. *Behavioural Brain Research*, **52**, 72–80.

Fowler, S.C. and Liou, J.-R. (1994) Microcatalepsy and disruption of forelimb usage during operant behavior: Differences between dopamine D_1 (SCH–23390) and D_2 (raclopride) antagonists. *Psychopharmacology*, **115**, 24–30.

Gallistel, C.R. and Karras, D. (1984) Pimozide and amphetamine have opposing effects on the reward summation function. *Pharmacology Biochemistry and Behavior*, **20**,73–77.

Gilbert, D.B. and Cooper, S.J. (1995) 7-OH-DPAT injected into the accumbens reduces locomotion and sucrose ingestion: D_3 autoreceptors-mediated effects? *Pharmacology Biochemistry and Behavior*, **52**, 275–280.

Grace, A.A. (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. *Neuroscience*, **41**, 1–24.

Graybiel, A.M., Aosaki, T., Flaherty, A.W. and Kimura, M. (1994) The basal ganglia and adaptive motor control. *Science*, **265**, 1826–1831.

Harris, R.A., Snell, D. and Loh, H.H. (1978). Effects of stimulants, anorectics, and related drugs on schedule-controlled behavior. *Psychopharmacology*, **56**, 49–55.

Hiroi, N. and White, N.M. (1991) The amphetamine conditioned place preference–Differential involvement of dopamine receptor subtypes and two dopaminergic terminal areas. *Brain Research*, **552**, 141–152.

Hoffman, D.C. (1989) The use of place conditioning in studying the neuropharmacology of drug reinforcement. *Brain Research Bulletin*, **24**, 373–387.

Hoffman, D.C. and Beninger, R.J. (1988) Selective D1 and D2 dopamine agonists produce opposing effects in place conditioning but not in conditioned taste aversion learning. *Pharmacology Biochemistry and Behavior*, **31**, 1–8.

Hoffman, D.C. and Beninger, R.J. (1989) The effects of selective dopamine D1 and D2 receptor antagonists on the establishment of agonist-induced place conditioning in rats. *Pharmacology Biochemistry and Behavior*, **33**, 273–279.

Hoffman, D.C., Dickson, P.R. and Beninger, R.J. (1988) The dopamine D2 receptor agonists, quinpirole and bromocriptine produce conditioned place preferences. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **12**, 315–322.

Hyland, B.I. (1999) Relationships of substantia nigra dopamine neurone activity to behaviour. In: R. Miller and J.R. Wickens (eds), *Brain dynamics and the striatal complex.* Conceptual Advances in Brain Research (series,) Reading: Gordon and Breach, in press.

Jackson, D.M., Jenkins, D.F. and Ross, S.B. (1988) The motor effects of bromocriptine: A review. *Psychopharmacology*, **95**, 433–447.

Josselyn, S.A., Miller, R. and Beninger, R.J. (1997) Behavioral effects of clozapine and dopamine receptor subtypes. *Neuroscience and Biobehavioral Reviews*, **21**,531–558.

Katz, J.L. and Witkin, J.M. (1992) Selective effects of the D_1 dopamine receptor agonist, SKF 38393, on behavior maintained by cocaine injection in squirrel monkeys. *Psychopharmacology*, **109**, 241–244.

Kebabian, J.W. and Calne, D.B. (1979) Multiple receptors for dopamine. *Nature*, **277**, 93–96.

Khroyan, T.V., Baker, D.A. and Neisewander, J.L. (1995) Dose-dependent effects of the D_3-preferring agonist 7-OH-DPAT on motor behaviors and place conditioning. *Psychopharmacology*, **122**, 351–357.

Kiyatkin, E.A. (1995) Functional significance of mesolimbic dopamine. *Neuroscience and Biobehavioral Reviews*, **19**, 573–598.

Kiyatkin, E.A. and Gratton, A. (1994) Electrochemical monitoring of extracellular dopamine in nucleus accumbens of rats lever-pressing for food. *Brain Research*, **652**, 225–234.

Kling-Petersen, T., Ljung, E., Wollter, L. and Svensson, K. (1995a) Effects of the dopamine D3- and autoreceptor preferring antagonist (-)-DS121 on locomotor activity, conditioned place preference and intracranial self-stimulation in the rat. *Behavioural Pharmacology*, **6**, 107–115.

Kling-Petersen, T., Ljung, E., Wollter, L. and Svensson, K. (1995b) Effects of dopamine D_3 preferring compounds on conditioned place preference and intracranial self-stimulation in the rat. *Journal of Neural Transmission*, **101**, 27–40.

Kötter, R. (1994) Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum. *Progress in Neurobiology*, **44**, 63–196.

LeMoal, M. and Simon, H. (1991) Mesocortical dopaminergic network: Functional and regulatory roles. *Physiological Reviews*, **71**, 155–234.

Leone, P. and Di Chiara, G. (1987) Blockade of D–1 receptors by SCH 23390 antagonizes morphine- and amphetamine-induced place preference conditioning. *European Journal of Pharmacology*, **135**, 251–254.

Lindvall, O. (1979) Dopamine pathways in the rat brain. In *The Neurobiology of Dopamine*, edited by A.S. Horn, J. Korf and B.H.C. Westerink, London: Academic Press, pp. 319–342.

Lopez, M., Balleine, B., and Dickinson, A. (1992). Incentive learning and the motivational control of instrumental performance by thirst. *Animal Learning and Behavior*, **20**, 322–328.

Lucki, I. (1983). Rate-dependent effects of amphetamine on responding under random-interval schedules of reinforcement. *Pharmacology, Biochemistry and Behavior*, **18**, 195–201.

Mackey, W.B. and van der Kooy, D. (1985) Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. *Pharmacology Biochemistry and Behavior*, **22**, 101–106.

Mallet, P.E. and Beninger, R.J. (1994) 7-OH-DPAT produces place conditioning in rats. *European Journal of Pharmacology*, **261**, R5–R6.

Martin-Iverson, M.T. and Fawcett, S.L. (1996) Pavlovian conditioning of psychomotor stimulant-induced behaviours: Has convenience led us astray? *Behavioural Pharmacology*, **7**, 24–41.

Mas, M., Fumero, B. and Gonzalez-Mora, J.L. (1995) Voltammetric and microdialysis monitoring of brain neurotransmitter release during sociosexual interactions. *Behavioural Brain Research*, **71**, 69–80.

Mazurski, E.J. and Beninger, R.J. (1986) The effects of (+)-amphetamine and apomorphine on responding for a conditioned reinforcer. *Psychopharmacology*, **90**, 239–243.

Mazurski, E.J. and Beninger, R.J. (1991) Effects of selective drugs for dopaminergic D1 and D2 receptors on conditioned locomotion in rats. *Psychopharmacology*, **105**, 107–112.

Messier, C., Mrabet, O. and Destrade, C. (1991a) Locomotor bias produced by intra-accumbens injection of dopamine agonists and antagonists. *Pharmacology Biochemistry and Behavior*, **41**, 177–182.

Messier, C., Mrabet, O., Durkin, T.P. and Destrade, C. (1991b) Bidirectional potentiation between D1 and D2 dopamine agonists–Effects of unilateral intra-accumbens injections on locomotor activity in mice. *Life Sciences*, **49**, 43–40.

Meyer, M.E. (1996) Mesolimbic 7-OH-DPAT affects locomotor activities in rats. *Pharmacology Biochemistry and Behavior*, **55**, 209–214.

Miller, R. and Beninger, R.J. (1991) On the interpretation of asymmetries of posture and locomotion produced with dopamine agonists in animals with unulateral depletion of striatal dopamine. *Progress in Neurobiology*, **36**, 229–256.

Miller, R., Wickens, J.R. and Beninger, R.J. (1990) Dopamine D–1 and D–2 receptors in relation to reward and performance: A case for the D–1 receptor as a primary site of therapeutic action of neuroleptic drugs. *Progress in Neurobiology*, **34**,1 43–183.

Möller, H.-G., Nowak, K. and Kuschinsky, K. (1987) Conditioning of pre- and post-synaptic behavioural responses to the dopamine receptor agonist apomorphine in rats. *Psychopharmacology*, **91**, 50–55.

Molloy, A.G. and Waddington, J.L. (1987) Assessment of grooming and other behavioural responses to the D–1 dopamine receptor agonist SK and F 38393 and its R- and S-enantiomers in the intact adult rat. *Psychopharmacology*, **92**, 164–168.

Morency, M.A. and Beninger, R.J. (1986) Dopaminergic substrates of cocaine-induced place conditioning. *Brain Research*, **399**, 33–41.

Nader, K., Bechara, A., Roberts, D.C.S. and van der Kooy, D. (1994) Neuroleptics block high- but not low-dose heroin place preferences: Further evidence for a two-system model of motivation. *Behavioral Neuroscience*, **108**, 1128–1138.

Neve, K.A. and Neve, R.L. (1997) Molecular biology of dopamine receptors. In *The Dopamine Receptors*, K.A. Neve and R.L. Neve (eds) , pp. 27–76. Totowa, NJ: Humana Press.

Niemegeers, C.E. and Janssen, P.A.J. (1979) A systematic study of the pharmacological activities of dopamine antagonists. *Life Sciences*, **24**, 2201–2216.

Niznik, H.B. and Van Tol, H.H.M. (1992) Dopamine receptor genes: New tools for molecular psychiatry. *Journal of Psychiatry and Neuroscience*, **17**, 158–180.

Phillips, A.G., Blaha, C.D. and Fibiger, H.C. (1989) Neurochemical correlates of brain-stimulation reward measured by ex vivo and in vivo analyses. *Neuroscience and Biobehavioral Reviews*, **13**, 99–104.

Pickens, R.W. and Crowder, W.G. (1967) Effects of CS-US interval on conditioning of drug response with assessment of speed of conditioning. *Psychopharmacology*, **11**, 88–94.

Pickens, R. and Harris, W.C. (1968) Self-administration of d-amphetamine by rats. *Psychopharmacology*, **12**, 158–163.

Pugh, M.T., O'Boyle, K.M., Molloy, A.G. and Waddington, J.L. (1985) Effects of the putative D–1 antagonist SCH23390 on stereotyped behavior induced by the D–2 agonist RU 24213. *Psychopharmacology*, **87**, 308–312.

Pycock, C.J. (1980) Turning behavior in animals. *Neuroscience*, **5**, 461–514.

Ranaldi, R. and Beninger, R.J. (1993) Dopamine D_1 and D_2 antagonists attenuate amphetamine-produced enhancement of responding for conditioned reward in rats. *Psychopharmacology*, **113**, 110–118.

Ranaldi, R. and Beninger, R.J. (1994) The effects of systemic and intracerebral injections of D1 and D2 agonists on brain stimulation reward. *Brain Research*, **651**, 283–292.

Ranaldi, R., Pantalony, D. and Beninger, R.J. (1995) The D1 agonist SKF 38393 attenuates amphetamine-produced enhancement of responding for conditioned reward in rats. *Pharmacology Biochemistry and Behavior*, **52**, 131–137.

Richardson, N.R., Piercey, M.F., Svensson, K., Collins, R.J., Myers, J.E. and Roberts, D.C.S. (1993) Antagonism of cocaine self-administration by the preferential dopamine autoreceptor antagonist, (+)-AJ 76. *Brain Research*, **619**, 15–21.

Robbins, T.W. (1977) A critique of the methods available for the measurement of spontaneous motor activity. In *Handbook of Psychopharmacology, Volume 7*, edited by L.L. Iversen, S.D. Iversen and S.H. Snyder, New York: Plenum Press, pp 37–82.

Robbins, T.W. (1981). Behavioural determinants of drug action: rate-dependency revisited. In *Theory in Psychopharmacology Volume 1*, edited by S.J. Cooper, London: Academic Press, pp. 1–63.

Robbins, T.W., Watson, B.A., Gaskin, M. and Ennis, C. (1983) Contrasting interactions of pipradol, d-amphetamine, cocaine, cocaine analogues, apomorphine and other drugs with conditioned reinforcement. *Psychopharmacology*, **80**, 113–119.

Scheel-Krüger, J. (1971) Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. *European Journal of Pharmacology*, **14**, 47–59.

Schultz, W., Dayan, P. and Montague, P.R. (1997) A neural substrate of prediction and reward. *Science*, New York, **275**, 1593–1599.

Self, D.W. and Stein, L. (1992) The D1 agonists SKF–82958 and SKF–77434 are self-administered by rats. *Brain Research*, **582**, 349–352.

Shippenberg, T.S., Bals-Kubik, R. and Herz, A. (1993) Examination of the neurochemical substrates mediating the motivational effects of opioids: Role of the mesolimbic dopamine system and D–1 vs. D–2 dopamine receptors. *Journal of Pharmacology and Experimental Therapeutics*, **265**, 53–59.

Shippenberg, T.S., Bals-Kubik, R., Huber, A. and Herz, A. (1991) Neuroanatomical substrates mediating the aversive effects of D–1 dopamine receptor antagonists. *Psychopharmacology*, **103**, 209–200.

Shippenberg, T.S. and Hertz, A. (1987) Place preference conditioning reveals the involvement of D_1-dopamine receptors in the motivational properties of m- and k-opioid agonists. *Brain Research*, **436**, 169–172.

Shippenberg, T.S. and Herz, A. (1988) Motivational effects of opioids: Influence of D–1 versus D–2 receptor antagonists. *European Journal of Pharmacology*, **151**, 233–243.

Sibley, D.R., Monsma, F.J., Jr. and Shen, Y. (1993) Molecular neurobiology of D_1 and D_2 dopamine receptors. In *D_1: D_2 Dopamine Receptor Interactions*, edited by J. Waddington, .London: Academic Press Limited, pp 1–17.

Skinner, B.F. (1938) *The Behavior of Organisms*, New York: Appleton-Century-Crofts.

Smith, A.D. and Bolam, J.P. (1990) The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurons. *Trends in Neurosciences*, **13**, 259–265.

Smith, I.D., Sutton, M.A. and Beninger, R.J. (1997) Rotational bias in intact rats following intrastriatal injections of dopaminergic drugs. *Pharmacology, Biochemistry and Behavior*, **58,** 431–441.

Stewart, J. (1992) Conditioned stimulus control of expression of sensitization of the behavioral activating effects of opiate and stimulant drugs. In *Learning and Memory: Behavioral and Biological Substrates*, edited by I. Gormezano and E.A. Wasserman, Hillsdale, N.J.: Lawrence Erlbaum Publishers, pp. 129–151.

Stewart, J. and Eikelboom, R. (1987) Conditioned drug effects. In *Handbook of psychopharmacology, Vol. 19: New directions in behavioral pharmacology*, edited by L.L. Iversen, S.D. Iversen and S.H. Snyder, New York: Plenum Press, pp 1–57.

Stewart, R.J., Morency, M.A. and Beninger, R.J. (1985) Differential effects of intrafrontocortical microinjections of dopamine agonists and antagonists on circling behaviour in rats. *Behavioural Brain Research*, **17**, 67–72.

Stoof, J.C. and Kebabian, J.W. (1981) Opposing roles for D–1 and D–2 DA receptors in efflux of cyclic AMP from rat neostriatum. *Nature*, London, **294**, 366–368.

Svensson, K., Carlsson, A., Huff, R.M., Kling-Petersen, T. and Waters, N. (1994a) Behavioral and neurochemical data suggest functional differences between dopamine D–2 and D–3 receptors. *European Journal of Pharmacology*, **263**, 235–244.

Svensson, K., Carlsson, A. and Waters, N. (1994b) Locomotor inhibition by the D_3 ligand R(+)–7-OH-DPAT is independent of changes in dopamine release. *Journal of Neural Transmission*, **95**, 71–74.

Tolman, E.C. (1949). The nature and functions of wants. *Psychological Review*, **56**, 357–369.

Ungerstedt, U. (1979) Central dopamine mechanisms and unconditioned behavoiur. In *The Neurobiology of Dopamine*, A.S. Horn, J. Korf and B.H.C. Westerink (eds), London: Academic Press, pp 577–596.

Vezina, P., Blanc, G., Glowinski, J. and Tassin, J.P. (1991) Opposed behavioural outputs of increased dopamine transmission in prefrontal and subcortical areas–A role for cortical D–1 dopamine receptor. *European Journal of Pharmacology*, **3**, 1001–1007.

Waddington, J.L. and O'Boyle, K.M. (1989) Drugs acting on brain dopamine receptors: A conceptual re-evaluation five years after the first selective D–1 antagonist. *Pharmacology and Therapeutics*, **43**, 1–52.

Weed, M.R., Vanover, K.E. and Woolverton, W.L. (1993) Reinforcing effect of the D_1 dopamine agonist SKF 81297 in rhesus monkeys. *Psychopharmacology*, **113**, 51–52.

Westerink, B.H.C. (1979) The effects of drugs on dopamine biosynthesis and metabolism in the brain. In *The Neurobiology of Dopamine*, A.S. Horn, J. Korf and B.H.C. Westerink (eds). London: Academic Press, pp 255–291.

Westerink, B.H.C. (1995) Brain microdialysis and its application for the study of animal behaviour. *Behavioural Brain Research*, **70**, 103–124.

White, N.M., Packard, M.G. and Hiroi, N. (1991) Place conditioning with dopamine–D1 and D2 agonists induced peripherally or into nucleus accumbens. *Psychopharmacology*, **103**, 271–270.

Wickens, J. (1990) Striatal dopamine in motor activation and reward-mediated learning: Steps towards a unifying model. *Journal of Neural Transmission*, **80**, 9–31.

Wickens, J. (1993) *A Theory of the Striatum*, Oxford: Pergamon Press.

Wickens, J. and Kötter, R. (1995) Cellular models of reinforcement. In *Models of information processing in the basal ganglia*, J.C. Houk, J Davis and D.G. Beiser (eds), Cambridge: MIT, pp 187–214.

Wise, R.A., Murray, A. and Bozarth, M.A. (1990) Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. *Psychopharmacology*, **100**, 355–361.

Wise, R.A. and Rompré, P.-R. (1989) Brain dopamine and reward. *Annual Review of Psychology*, **40**, 191–227.

Woolverton, W.L. (1986) Effects of a D_1 and a D_2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. *Pharmacology Biochemistry and Behavior*, **24**, 531–536.

Woolverton, W.L., Goldberg, L.I. and Ginos, J.Z. (1984) Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics*, **230**, 678–683.

Young, S.D. and Michael, A.C. (1993) Voltammetry of extracellular dopamine in rat striatum during ICSS-like electrical stimulation of the medial forebrain bundle. *Brain Research*, **600**, 305–307.